REMARKS/ARGUMENTS

Upon entry of the instant reply, claims 2-92 will remain pending, with claims 2, 4, 16, 17, 18, 19, 28, 32, 38, 43, 48, 54, 59, 63, 67, 73, 78, 83 and 88 being independent claims.

In contrast to the indication in the Office Action, claims 2-92 are pending in this application. In particular, claims 2-18 are under prosecution, and claims 19-92 should be indicated to be withdrawn from consideration as being directed to non-elected inventions.

Consideration Of Disclosure Statements

In the previous response, Applicants expressed appreciation for the inclusion with the Office Action of copies of the Forms PTO-1449 submitted with the disclosure statements filed July 16, 2001, October 3, 2001, November 3, 2001, November 28, 2001 and August 19, 2002, whereby the Examiner's consideration of these disclosure statements is of record. However, it was noted that upon review of the Forms PTO-1449 attached to the Office Action:

(a) The Form PTO-1449 submitted with the disclosure statement filed November 5, 2001 which cites CHANG et al. is not initialed. Therefore, Applicants submitted a Form PTO-1449 once again listing this document.

(b) The Form PTO-1449 submitted with the disclosure statement filed October 3, 2001 is apparently inadvertently not initialed at Citation No. 3 to LEIBOVICH et al.. Accordingly, the Form PTO-1449 submitted by Applicants once again listed this document.

(c) The Form PTO-1449 submitted with the disclosure statement filed July 16, 2001, on Sheet 2 of 10, has crossed out Citation No. 1 to BANERJEE, "Angiogenesis: Characterization of a Cellular Model", Puerto Rico Hlth. Sci., J., 17, 327-333. Applicants pointed out that there is no indication as to why this document is crossed through. However, it was noted that a publication date was not included on the form. Applicants therefore included the publication date of January 1999 on the Form PTO-1449 submitted with the last response.

(d) The Form PTO-1449 submitted with the disclosure statement filed July 16, 2001, on Sheet 4 of 10, has crossed out Citation No. 34 to KESSLER et al., "Mast Cells and Tumor Angiogenesis", Intern. J. Can., 18, 703-709 (1976) as being illegible. Applicants therefore submitted another copy with the previous response, and listed the document on the submitted Form PTO-1449.

(e) The Form PTO-1449 submitted with the disclosure statement filed July 16, 2001 is apparently inadvertently not initialed at Sheet 6 of 10, Citation No. 55, Nguyen et al. Accordingly, the Form PTO-1449 submitted with the last response once again listed this document.

Applicants therefore respectfully requested in the previous response that the Examiner initial the Form PTO-1449 submitted herewith to indicate consideration of each of the documents. The Examiner was requested to forward an initialed copy of the form to Applicants with the next communication from the Patent and Trademark Office, and to charge any fees required in this connection to Deposit Account No. 19-0089.

Despite the above, the Final Office Action neither mentioned the disclosure statements nor included an initialed copy of the Form PTO-1449 attached thereto. Therefore, Applicants respectfully request that an initialed copy of the form be forwarded with the next communication from the Patent and Trademark Office. For the Examiner's convenience another copy of the Form PTO-1449 is submitted herewith.

Claim For Domestic Priority

Applicants note that in the previous response it was requested that the Examiner acknowledge the claim of domestic priority. In particular, Applicants respectfully requested that the Examiner acknowledge the claim for domestic priority under 35 U.S.C. 119(e) to provisional Application No. 60/181,312. Despite this request, the present Final Office Action has not acknowledged the claim of domestic priority. **Therefore, the Examiner is respectfully requested to acknowledge the claim of domestic priority in the next communication from the Patent and Trademark Office.**

Request For Approval Of Drawing Corrections

In their previous response, Applicants requested that the Request for Examiner Approval of Drawing Amendment filed September 12, 2001 be acknowledged, and that the drawing change requested therein be approved. Despite this request, the Final Office Action has neither acknowledged the Request for Examiner Approval of Drawing Amendment nor indicated approval of the drawing change. **Therefore, the Examiner is respectfully requested to**

acknowledge the Drawing Amendment as well as its approval in the next communication from the Patent and Trademark Office.

Response To Restriction Requirement

Applicants note that the Final Office Action is silent with respect to the Restriction Requirement and the non-elected claims. Therefore, to ensure that the record is complete, Applicants note that the restriction of Groups IV-XIV is maintained and has been made Final. Claims 19-92 stand withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Applicants note that they are once again permitting non-elected claims 19-92 to remain pending subject to possible rejoinder upon allowance of the elected claims.

Request To Withdraw Finality Of Office Action

Applicants respectfully submit that the rejection of claims 2-18 under 35 U.S.C. 103(a) as being unpatentable over Banerjee et al.(hereinafter "Banerjee"), Indian J. of Biochem. and Biophysics, Vol.. 30(6), pp. 389-94 and Tiganis et al. (hereinafter "Tiganis"), Exp. Cell Research, Vol. 198, pp. 191-200 (1992) was not included in the previous Office Action, and is raised upon claims in the present Final Office Action that could have been rejected over these documents. In other words, Applicants' amendment **did not necessitate the new grounds of rejection set forth in the present Final Office Action.**

The Examiner is reminded that, under present Patent and Trademark Office practice, an Office Action should not be made final where the examiner introduces a new ground of rejection therein that is neither necessitated by Applicants' amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

In the instant situation, claim 2 was amended to be in independent form. Certainly, such an amendment to place a claim into independent form cannot be considered to be an amendment that necessitated a new ground of rejection. The issues relative to claim 2 are the same prior to as well as after Applicants' amendment.

Therefore, this new ground of rejection was not necessitated by Applicants' amendment. Accordingly, the finality of the Office Action is premature, and should be withdrawn in the event that the application is not allowed in response to the instant response.

Response To Rejections Based Upon Prior Art

As noted above, claims 2-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banerjee, Indian J. of Biochem. and Biophysics, Vol.. 30(6), pp. 389-94 and Tiganis, Exp. Cell Research, Vol. 198, pp. 191-200 (1992).

In this ground of rejection, the rejection makes various inappropriate assumptions regarding the disclosures of each of Banerjee and Tiganis, improperly combines the disclosures of these two documents, and arrives at a combination of these documents that is not taught or suggested in the prior art.

In response, Applicants initially remind the Examiner that the disclosure set forth in Banerjee is directed to a study of dependence of protein N-glycosylation on capillary endothelial cell proliferation. The study indicates that amphomycin, a potent N-glycosylation inhibitor, inhibited capillary endothelial cell proliferation in a dose-dependent manner. The study is also indicates that the β-agonist isoproterenol as well as other intracellular cAMP enhancing agents also enhance capillary endothelial cell proliferation. **The study of Banerjee does not teach or suggest that tunicamycin inhibits capillary endothelial cell proliferation.**

The study of Banerjee also states that, in addition to cell proliferation, isoproterenol also enhanced protein glycosylation in these cells. It is noted in the study that isoproterenol effect was mediated by β-adrenoreceptors, as it got reduced on pre-treatment of cells with either atenolol or ICI 118, 551 or propranolol.

The study further states that isoproterenol stimulation of protein glycosylation by exogenous dolichyl monophosphate and its inhibition by tunicamycin (GlcNAc-1P transferase inhibitor) supported the concept that isoproterenol specifically stimulated protein N-glycosylation event(s) in the cell. Accordingly, **tunicamycin is studied in Banerjee with respect to its effect on isoproterenol interactions, and not with respect to its effect on glycosylation and/or angiogenesis**.

For example, at page 391 of Banerjee, the **effect of amphomycin** on endothelial cell proliferation and regulation of protein glycosylation by β-adrenoreceptor stimulation is studied. Moreover, Table 3 shows the effect of amphomycin on capillary endothelial cell doubling time and growth rate. In particular, Table 3 illustrates that at an increasing concentration of

amphomycin, the growth rate (% over control) is decreased, whereby inhibition of growth is illustrated.

Following this discussion, Banerjee then discusses the effect of Dol-P, Dol-P plus tunicamycin, and propranolol on isoproterenol-mediated protein glycosylation with results being indicated in Table 6. Table 6 illustrates the effect of Dol-P, Dol-P + tunicamycin, and propranolol on isoproterenol-mediated protein glycosylation. As can be seen in the Table 6, there is measurement of the rate of mannose to leucine in the control and in isoproterenol treated cells. The study is aimed at the evaluation of isoproterenol, and utilizes differing materials in the study. **This Table illustrates the effect of tunicamycin on the actual materials being studied in Banerjee, and not with respect to the effect of tunicamycin on glycosylation and/or angiogenesis.**

There is no teaching or suggestion in Banerjee's study of the presently claimed invention. **The Examiner is once again reminded that the rejection cannot merely look to the occurrence of single words in a document, but must ascertain what the document teaches or suggests with respect to a combination of the words, and especially what the reference teaches as a whole.** Under the present circumstances, Banerjee does not teach or suggest, Applicants disclosed and claimed invention. For example, **Banerjee does not teach or suggest inhibiting angiogenesis using a nucleoside comprising glucosamine or a nucleoside comprising a pyrimidine nucleoside let alone tunicamycin and functional derivatives thereof.**

In an attempt to overcome the deficiencies of Banerjee, the rejection relies upon Tiganis. However, Tiganis is directed to a system for academic purposes and this system relates to aortic endothelial cells. These cells do not form capillaries, and are not associated with vascular or tumor growth. **Therefore, in contrast to the assertions in the rejection of record, Tiganis does not support any recognition in the prior art of the disruption of vascular proliferation or angiogenesis using tunicamycin.** In contrast to the assertions in the rejection, Tiganis does **not** teach that inhibition of glycoproteins by tunicamycin impairs the cell adhesion and the functional properties of the endothelial lining of the blood vessels. Thus, in contrast to the assertions in the rejection, one of skill in the art would not have a reasonable expectation of success that tunicamycin is useful as an agent for inhibiting angiogenesis.

Still further, Tiganis discloses killing cells using tunicamycin, and reviewing cell death over a period of days. For example, attention is directed to Tiganis, page 197, left-hand column, under the heading "Cell Growth". In the discussion section of Tiganis, such as disclosed at page 198 at the paragraph beginning at the end of the page, tunicamycin is disclosed to have inhibited the growth and was cytotoxic for dividing endothelial cells but as not inhibiting the growth and not being cytotoxic for confluent cells.

Still further, Tiganis discloses in the last two paragraphs on page 199, that tunicamycin is expected to cause damage to brain microvessels which is likely due to a direct action of tunicamycin on the endothelial cells. Thus, Tiganis does not provide any disclosure of therapeutic use, and, in fact, warns in the concluding portion of his Discussion section about damage to brain microvessel endothelial cells. Therefore, it is apparent that Tiganis discloses

that it would be expected that the animal would be killed or suffer neurological disorder. Accordingly, there is no expectation of success.

Expanding upon the above, it is noted that Banerjee is studying compounds completely different than tunicamycin. For example, Banerjee is studying compounds such as amphomycin which is a completely different compound, and has a different mechanism in blocking cell growth. Moreover, as noted above, Table 6 of Banerjee is a continuation of the study of the compounds which are different from tunicamycin, and summarizes that cAMP stimulates the protein N-glycosylation. Tunicamycin is used as an inhibitor to block protein N-glycosylation, and only shows that cAMP stimulates the protein N-glycosylation and angiogenesis and mechanism. Tunicamycin is only used because of its ability to block protein N-glycosylation.

From the above, it is apparent that there is no expectation of success. For example, Applicants' invention is directed to inhibiting angiogenesis which includes programmed cell death and not cytotoxicity. Applicants' invention is not directed to killing cells by cytotoxicity, such as disclosed by Tiganis.

The Examiner is reminded that when applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

Under the present circumstances, consideration of the claimed invention as a whole and the documents of record as a whole clearly indicates that Applicants' disclosed and claimed invention is different from any combination of the prior art. Moreover, any combination of the prior art, even if appropriate, would not arrive at Applicants' disclosed and claimed invention. Still further, there is no reasonable expectation of success following the disclosures of Banerjee and Tiganis.

Therefore, independent claim 2 patentably recites a method for inhibiting angiogenesis, comprising administering a nucleoside in an amount effective to inhibit angiogenesis, to a patient in need of such treatment, the nucleoside comprising glucosamine.

Dependent claim 3 further patentably defines that the glucosamine comprises N-acetylated glucosamine.

Independent claim 4 patentably defines that a method for inhibiting angiogenesis, comprising administering a nucleoside in an amount effective to inhibit angiogenesis, to a patient in need of such treatment, the nucleoside comprising a pyrimidine nucleoside.

Dependent claim 5 further patentably defines that the glucosamine comprises at least one of tunicamycin and functional derivatives thereof.

Dependent claim 6 further patentably defines that the glucosamine is represented by the recited formula.

Dependent claim 7 further patentably defines that the glucosamine comprises at least one of tunicamycin homologues A_1, A_2, B_1, B_2, C_1, C_2, D_1, and D_2.

Dependent claim 8 further patentably defines that the glucosamine is administered for a period of time, subsequently the administration of the glucosamine is suspended for a period of time of at least about 1 week, and subsequently the administration of the glucosamine is resumed.

Dependent claim 9 further patentably defines that the at least one of tunicamycin and functional derivatives thereof is administered for a period of time, subsequently the administration of the at least one of tunicamycin and functional derivatives thereof is suspended for a period of time of at least about 1 week, and subsequently the administration of the at least one of tunicamycin and functional derivatives thereof is resumed.

Dependent claim 10 further patentably defines that the glucosamine is administered for a period of about 1 week to 6 months.

Dependent claim 11 further patentably defines that the glucosamine is administered for a period of about 1 week to 6 months, subsequently the administration of the glucosamine is suspended for a period of about 1 week to 1 year, and subsequently the glucosamine is administered for a period of about 1 week to 6 months.

Dependent claim 12 further patentably defines that the glucosamine is administered daily in a dosage of about 5 to 20 mg/kg of body weight.

Dependent claim 13 further patentably defines that the glucosamine is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight, subsequently the administration of the glucosamine is suspended for a period of about 1 week to

6 months, and subsequently the glucosamine is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight.

Dependent claim 14 further patentably defines that the glucosamine comprises at least one of tunicamycin and functional derivatives thereof.

Dependent claim 15 further patentably defines that the patient in need of such treatment has at least one of diabetic retinopathy, atherosclerotic plaques, scleroderma, hypertrophic scarring, vascular adhesions, angiofibroma, trachoma graft neovascularization, corneal graft neovascularization, neovascular glaucoma, thrombosis, restenosis, osteoporosis, macular degeneration, arthritis, hemangiomas, psoriasis, and a tumor.

Dependent claim 16 patentably defines a method for inhibiting angiogenesis, comprising administering a nucleoside, which comprises glucosamine, in an amount effective to inhibit angiogenesis, to a patient in need of such treatment; wherein the nucleoside is administered for a period of time, subsequently the administration of the nucleoside is suspended for a period of time of at least about 1 week, and subsequently the administration of the nucleoside is resumed.

Dependent claim 17 patentably defines a method for inhibiting angiogenesis, comprising administering a nucleoside in an amount effective to inhibit angiogenesis, to a patient in need of such treatment; wherein the nucleoside is represented by the recited formula; wherein the nucleoside is administered for a period of time, subsequently the administration of the nucleoside is suspended for a period of time of at least about 1 week, and subsequently the administration of the nucleoside is resumed.

Dependent claim 18 patentably defines a method for inhibiting angiogenesis, comprising administering tunicamycin in an amount effective to inhibit angiogenesis, to a patient in need of such treatment; wherein the tunicamycin is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight, subsequently the administration of the tunicamycin is suspended for a period of about 1 week to 6 months, and subsequently the tunicamycin is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight.

Applicants therefore respectfully submit that the prior art of record does not teach or suggest their disclosed and claimed invention. Accordingly, the rejections of record are without appropriate basis, and should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow all the pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions or wish to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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